

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

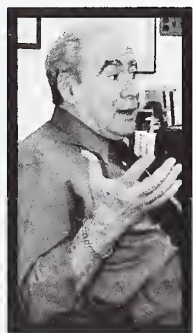
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From the Cloning Frontier

CLONE RANGERS UP AGAINST A 'WALL'

by Celia Hooper

Norton Zinder, retired (but unretiring) virologist from New York's Rockefeller University and a member of the National Academy, has ventured to the Wild West-like frontier of mammalian cloning and has a story for NIH: "There's hard, good, interesting science there,"



Fran Pollner

Norton Zinder

he says, but the people working in the field, by and large, are not pursuing it.

Zinder recently co-organized a meeting, "Mammalian Cloning: Biology and Practice," that brought together—in many instances, for the first time—the biggest names in cloning. Speakers included Ian Wilmut and former colleagues who created Dolly (see *The NIH Catalyst*, May-June 1997, page 1); cloners of mice, pigs, and cows; would-be cloners of rats and primates; basic scientists studying early development; and a few philosophers of science. Co-organizers of the meeting, held March 12–15 at the Cold Spring Harbor (N.Y.) Banbury Center, were Peter Mombaerts, also of Rockefeller; Neal First, of the University of Wisconsin, Madison; and Jan Witkowski, Banbury Center director. In early May, Zinder came to NIH to discuss the meeting informally with NIH scientific leaders and colleagues.

"There are so many questions!" Zinder raves. "There's new science to be found." But, unfortunately, what is steering the research, he con-

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Nobelist Baruch Blumberg on a Mission to NIH ASTROBIOLOGY AND THE SEARCH FOR ORIGINS

by Fran Pollner

Shortly after Baruch Blumberg came to NIH in 1957, he and others in the clinical research group he'd joined (in what was then known as the Arthritis and Metabolic Diseases Institute) started a new section. It was Blumberg who named the new section "Geographic Medicine and Genetics."

"Thinking of genes by themselves can be misleading," he explains. "You can't look at just one gene at a time and you can't look at genes outside the context of the environment of the host, both internal and external."

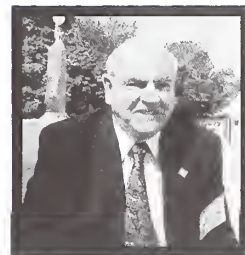
The world at large became the site of his field work studying polymorphisms and their relation to disease susceptibility—work that led to the discovery of the Australia antigen and later, after he'd left NIH, to the identification of the hepatitis B virus and the development of the hepatitis B vaccine.

Today, Blumberg's focus is still, essentially, "geographic medicine and genetics," but his "geography" has expanded beyond the terrestrial.

Last spring, Blumberg became the first director of the newly created NASA Astrobiology Institute (NAI). Its mission is the "study of the origin, evolution, distribution, and future of life on earth and in the universe." Headquartered at the Ames Research Center in Mountain View, Calif., its work is carried out wherever the spirit moves affiliated scientists at what are now 11 participating U.S. institutions and one international team. And, like the universe, the NAI is expandable.

Blumberg would especially like to see expansion in the form of coordinated NAI-NIH research. He envisions a variety of collaborations to be determined between NAI and NIH intramural sci-

tists—jointly funded projects, perhaps, in such areas as new and emerging diseases, prebiotic chemistry, and the origins of cancer. He's had discussions with acting NIH director Ruth Kirschstein, deputy director for intramural research Michael



Fran Pollner

Baruch Blumberg,
director, NASA
Astrobiology Institute

Gottesman, and NIAID director Tony Fauci, and he plans to talk with more institute heads. Discussions are under way for an NAI-NIH seminar to acquaint the scientific community here with the astrobiological plane.

It's a program of "discovery, of basic research," Blumberg says. And although much of the research "is based on the notion that NASA has space flight capabilities,"

most of it to date has actually been conducted on Earth—albeit under the sea,

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CYBERSPACE PUBLISHING AND THE IRP: 'E' IS FOR EXCELLENCE—AS USUAL



Michael Gottesman

Earlier this year, I forwarded to the institute directors, scientific directors, and executive officers the report of a committee on electronic publishing. The committee was chaired by Henry Metzger (NIAMS) and included Robert Nussenblatt (NEI), Ed Liu (NCI), Annette Wysocki (NINR), Eugene Koonin (NLM), and Celia Hooper (OIR). This report has been discussed and has the concurrence of the Board of Scientific Directors. It is printed below.

The report includes the following recommendations, which I support:

- Approval of manuscripts submitted for electronic publication will require the same process as is currently used for printed publications.

- NIH intramural scientists who wish to establish electronic journals, as either official duty or outside activities, may do so following an approval process at the IC level.

- The scientific directors will monitor and keep track of creation of electronic journals by intramural scientists and of submission of data to non-peer-reviewed electronic sites and report these events to the deputy director for intramural research (DDIR) on the Management Control Checklist.

The DDIR will, in turn, ascertain whether such electronic publications remain in keeping with the principle stated in the "Guidelines for the Conduct of Research in the Intramural Research Program at NIH" that "All research staff in the Intramural Research Programs should maintain exemplary standards of intellectual honesty in formulating, conducting, and presenting research, as befits the leadership role of the NIH."

—Michael Gottesman, Deputy Director for Intramural Research

REPORT OF THE COMMITTEE ON ELECTRONIC PUBLISHING

I. Introduction

The "Guidelines for the Conduct of Research in the Intramural Research Program at NIH" state, "All research staff in the Intramural Research Programs should maintain exemplary standards of intellectual honesty in formulating, conducting, and *presenting* research, as befits the leadership role of the NIH." (emphasis added)

The deputy director for intramural research, NIH, asked the committee to consider whether the increased use of electronic publishing in general, and the establishment of PubMed Central in particular, required additional regulatory or monitoring mechanisms to complement those already in place with respect to conventional publication activities of the intramural scientific staff (see "Current Procedures for Overview of Publishing Activities by NIH Staff").

The committee feels that the electronic promotion of easy access to full-text material in conventionally published journals raises no new issues. However, the enhanced possibilities that electronic publishing permits for the easier establishment of new journals and the publication of materials that might not otherwise be published, given the constraints of conventional "hard copy" publishing, deserve consideration. The relative expense of conventional publishing usually necessitates the involvement of substantial organizations with a self-interest in maintaining high quality. The new opportunities for facily disseminating information electronically could potentially lead to the flooding of the scientific literature with trivial and possibly even misleading material.

II. Is the NIH Intramural Research Program (IRP) a Special Case?

NIH is appropriately perceived by many as a source of credible and even official or "certified" information. It therefore has a self-interest in protecting its reputation in that regard. Another germane aspect is that the public and even many professionals often do not appreciate that the IRP is completely divorced from the decision-making process by which extramural research is funded. Thus any involvement by IRP scientists in the publication of research that can even give the appearance of promoting or suppressing the support of biomedical research in general should be avoided.

III. Who Should Act as Gatekeeper?

The decentralized organization of NIH into multiple ICs leads to a diversity of approaches to fostering biomedical research and is one of its great strengths. Nevertheless, much of the public and even many professionals think of NIH as a whole, and therefore lapses by individual members of an institute or center reflect not only on that particular IC but on NIH as a whole.

With respect to the new issues created by PubMed Central, the satisfactory solution that has been developed to resolve these nominally conflicting concerns in other contexts should be followed, that is, the Office of Intramural Research (OIR) should establish guidelines to which each IC will be expected to adhere, using whatever mechanisms it deems most appropriate. Periodically, the OIR should monitor these activities as part of the Management Control Checklist. For

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CONGRATULATIONS!



Fran Pollner

Smile and the world smiles with you: Reed Wickner (left) and Leslie Ungerleider are two illustrious additions this year to the National Academy of Sciences. Wickner, chief of the NIDDK Laboratory of Biochemistry and Genetics, grinned as he acknowledged, "I am very happy about this, to tell the truth." And Ungerleider, chief of the NIMH Laboratory of Brain and Cognition, happily described herself as "overwhelmed." She also noted that last year at this time, it was her husband (Robert Desimone, also at NIMH) who was elected to the Academy.

CATALYTIC RELOCATIONS

The NIH Catalyst has moved on! After bouncing around Building 1 since its birth in 1993, the Catalyst has finally moved into custom-made and hopefully permanent quarters in the newly reopened Building 2. Catty-cornered from Building 1, Building 2 also houses other arms of the OIR—the Office of Loan Repayment and Scholarship and the Office of Education, as well as the Office of AIDS Research and OD executive offices.

We are on the second floor in rooms 2W23 and 27. Phone, fax, and e-mail remain the same.

Our parallel universe has also moved—the new web address for the Catalyst is

<<http://catalyst.cit.nih.gov/catalyst/>>. There you will find the first two issues of the year 2000 (and by mid-June this



Jim Alexander

Party of Five (left to right): Catalyst scientific editor Celia Hooper, outfitted for the occasion to achieve "better reception," contributing editor Katie Farr (NIDDK), contributing writer Cynthia Delgado (NCI), incoming Catalyst intern Peggy Coulombe NINDS, and Catalyst managing editor Fran Pollner

very issue) and previous issues that reach back to May 1994. All of 1999 is currently missing but will magically materialize before 2001. We promise. ■

CIVIL Defense Against Workplace Violence

NIH is committed to providing a work environment that is free from violence, threats of violence, harassment, intimidation, and other disruptive behavior. NIH is fortunate to have had relatively few reported violence problems. However, no workplace is immune.

As reflected in policy statements issued in 1998 and again on March 1, 2000, it is NIH policy that disruptive behavior will be dealt with swiftly and firmly. To help the NIH community prevent and respond to workplace threats and violence, the NIH director recently established a coordinated resource collectively named CIVIL. A major component of CIVIL is the Response Team, which:

- Advises ICs regarding intimidating, harassing, disruptive, or dangerous workplace behavior
- Investigates threats
- Intervenes in crisis situations
- Identifies resources to provide employee counseling in the aftermath of violence,
- Provides a coordinated response from staff including the NIH Ombudsman, Employee Assistance Program (EAP) Consultants, Employee Relations Specialists, and the NIH Police.

When there is immediate danger, always call the police first:

Call 911, if at Bethesda campus

Call 9-911, if at other NIH site

Call CIVIL when:

- You need help assessing the potential seriousness of a threatening situation;
- You are experiencing a threatening situation at work and need intervention from trained staff;
- You become aware of a workplace situation involving intimidating, harassing, or other unproductive or dangerous behaviors and need consultation
- You need help in addressing your own aggressive reactions to a workplace situation; or
- A situation involving threats or aggressive acts already has occurred and you need assistance managing the aftermath and its effect.

Anyone can call CIVIL:

On campus, call C-I-V-I-L (2-4845); off-campus, call 9-301-402-4845.

For additional information, check out the CIVIL web site at:

<<http://civil.nih.gov/>>.

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tends, is not interest in fundamental mechanisms in development, but goals such as making sheep that produce Factor IX or pigs whose histocompatible organs can be transplanted into humans. Others at the conference say this characterization is unfair. Logistics—the cost of maintaining a herd of large animals and their longer gestation periods—make these models impractical for solving basic research questions compared to the mouse, which in turn is a recent and difficult cloning subject.

Zinder says the central mystery emerging from cloning is what he calls “the wall”—the extremely low success rates in producing viable cloned mammals. In the species that have been cloned—sheep, mice, pigs, goats, and cows—the very best cloning techniques typically produce in the neighborhood of one or two newborn animals for every 100 oocytes in which nuclear transfer is attempted. Some species, including primates, rabbits and rats, cannot be cloned by any nuclear transfer techniques tried to date. (Identical animals of these and other species have been produced by splitting apart embryos after just a couple of cell divisions.) The cloned animals that are born are sometimes abnormally large with large placentas. They are beset with respiratory and immunological problems and, typically, half of the newborn clones die in their first days of life.

To clone a mammal, scientists typically start with ripe oocytes from which they have removed the nucleus via micropipette. How much permanent damage is done to the host egg cell during enucleation is unknown. Replacement nuclei are then inserted into the oocytes or enter when a diploid donor cell is fused to the oocyte. The oocyte is stimulated with a chemical or electrical shock, then allowed to develop to the blastula stage in vitro.

The donor cells and nuclei usually come from fetal fibroblasts or Sertoli or cumulus cells—the layers of parent cells that feed sperm- and oocyte-generating cells, respectively. Other adult-derived nuclei may also be “competent” to progress all the way through development to live birth, but Zinder says the exact nature of such cells and compe-

tence is unknown. Also unknown, he says, are the optimal cell cycle stages for host cell and donor nucleus. He says there is some hint that these must match.

Most of the altered oocytes will not reach the blastula stage. Those that do are implanted in a surrogate mother. The hurdles do not end there. Implanted embryos may perish at any of a number of points before birth with defects in placenta formation and a wide array of organ systems. While these events may discourage cloners, Zinder

sees a gold mine in such failures. He suspects cloned animals that fail to develop properly could shed light on epigenetic factors important to development.

Zinder throws up his hands in exasperation when asked simple questions about the causes of “the wall” that are being brushed off in the scurry to clone transgenic animals. What is the role of methylation and appropriate “programming” of genes in the somatic nuclei that are transferred into the enucleated oocytes? Is telomere length a factor? How important are accumulated somatic mutations and the overall state of repair of the DNA from donor nuclei?

How important are the mitochondria and the hoards of mRNA packed into oocyte cytoplasm? “They don’t know,” Zinder maintains. It’s not even clear whether “the wall” is the result of one or two major problems, or an accumulation of numerous insults to recipient oocyte and donor nucleus, he says.

Based on indirect evidence in the mouse from Rudolf Jaenisch’s lab at MIT, Zinder says he suspects imprinting anomalies are a key problem. In a paper by Tucker et al. (*Genes & Devel.* **10**, 1008, 1996), the group showed that post-zygotic nuclei—



Fran Pollner

There's gold in them thar failures, Zinder observes.



Fran Pollner

For Zinder, to solve the mystery of the competent nucleus is far more alluring, than, say, creating animal drug factories.



Fran Pollner

'Who knows?' seems to be the answer to scores of crucial questions, Zinder says.

which should presumably include donor nuclei in clones—lack the enzymatic machinery to reset the methylation on imprinted genes they examined—in contrast to nonimprinted genes. During implantation, nonimprinted genes undergo massive demethylation and re-

methylation, correcting random demethylation errors that accumulate over time. Random demethylation hits to imprinted genes—normally corrected during gametogenesis—would not be fixed. “At this point, disturbed imprinting seems to be a plausible hypothesis that could explain the frequent late gestation failure of clones,” Jaenisch told *The NIH Catalyst* via e-mail. “But we need to get direct evidence for it.”

In a *PNAS* article in February, Mario Capecchi of the University of Utah in Salt Lake City proposes that how quickly the egg begins to divide—or more correctly, how fast the nucleus must be reprogrammed—might explain why cloning mice appears to be even less successful than cloning larger animals. Capecchi writes, “One factor that might contribute to a difference in cloning efficiency is a possible timing difference associated with the very early cell divisions as to how rapidly the zygotic gene products are required to sustain normal development in various species.”

One of the biggest hits at the Cold Spring Harbor symposium, Zinder says, was a technique discussed by Eric

Overstrom of Tufts University School of Veterinary Medicine in North Grafton, Mass. Unpublished experiments in Overstrom’s lab suggest that demecolcine can be used to enucleate oocytes chemically, and perhaps more gently, than a micropipette. Application of the substance to oocytes caused them to jettison their nuclei, Zinder says, adding that other labs are

studying whether chemical enucleation can improve cloning success rate.

Another concern of cloners—that clones derived from nuclei from aged somatic cells would prove to be geneti-

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cally "old"—was dissipated by an article in *Science* just days before Zinder visited NIH. Robert Lanza at Advanced Cell Technology, Worcester, Mass., and colleagues, reported that the group cloned six calves from senescent donor cells. The donor nuclei were derived from fetal calf cells that had been dividing in culture for several months. When the cells were within 0 to 2 divisions of their expected life span, the scientists extracted almost 1,900 nuclei and transplanted them to oocytes. The six calves that resulted were healthy at 2 months of age. The telomeres of the calves' cells were measured 5 to 10 months after birth and actually appeared longer than telomeres of normally bred calves. A news story in the same *Science* issue indicates that unpublished reports from other labs will confirm the telomere finding.

NIDCD director James Battey, who attended the cloning meeting, says that although they were not well represented at the meeting, "There are a lot of people interested in the mechanisms that underlie reprogramming of the nucleus in development." The mix of people at the conference was perhaps too heavily weighted toward applied science "given our profound ignorance of reprogramming within the nucleus." Battey says he does not begrudge the cloners their single-minded pursuit of efficient, cost-effective nuclear transfer because the therapeutic uses of cloned transgenics "could contribute to the health of the nation in a big way." But Battey thinks that ultimately the cloners will need to address "the wall."

"The overall answer to making cloning efficient," he observes, "will come from understanding the basic mechanisms in silencing expression of genes in a somatic cell" and then converting the cell's program to pluripotency—the ability to recapitulate the entire development of an organism.

Reflecting on his sojourn in the wild world of cloning, Zinder says he is now headed in other directions and won't be roped in to any more roundups. He has urged the cloners to plan a more open meeting next time, one that could attract more early-career and basic scientists. "I'd like to get [scientists] interested in this as a way to look at developmental biology. The field is interesting in ways other than most current practitioners see it," he says. "The only way to do new science is to get the kids into it—the postdocs and grad students." ■

deep within rocks, or embedded in ice, for example. Some of the materials studied traveled through space to get here.

"Astrobiologists are very interested in organisms that live under what we think of as extreme conditions; of course, they are not 'extreme' for these organisms, which we have given the name 'extremophiles.'"

The greatest probability for life in our solar system, Blumberg says, is on Mars, Europa (a moon of Jupiter), and Titan (a moon of Saturn), as well as in "cosmic dust," which can also be found all over Earth. If life actually exists in these places, it would most likely be under the conditions of early Earth, before our atmosphere had oxygen, when extremophiles probably flourished here, he says.

"We want to look at early Earth and the organisms that are still present in contemporary geothermal vents," he notes, observing that although such astrobiological explorations may seem remote, "the whole world of molecular biology, as revealed by PCR, is based on an enzyme extracted from an extremophile that operates at very high temperatures"—a discovery that earlier generated considerable interest in the field of astrobiology.

Some life forms adore the cold. "A lot of our people are in the Arctic and Antarctic, where they have found organisms living in ice crystal water channels. Nobody knows if they cause disease. I'm interested in exploring virology, the phage within these bacteria under these extreme conditions."

Medical microbiologists and astrobiologists, Blumberg notes, tend to look at organisms differently. The "one bug—one disease" paradigm still prevails among the former, while the latter adopt an "ecological approach," examining, for example, biofilms, or layers of bacteria



Fran Pollner

Baruch Blumberg in town for the National Academy of Sciences annual meeting and to talk about astrobiology.

glued together with long-chain sugars, and the interactions among organisms and the relation of their evolution to the changes in the earth's environment.

Another possible field for mutual exploration, presumably with NCI, could revolve around the question, "When did cancer start?" The answer could be, "When cells first started," Blumberg speculates. How cells started is a major astrobiological concern. The search for organic matter in space has uncovered such things as amino acids in meteorites and organic molecules floating freely in space dust. "There's a lot going on in prebiotic chemistry," Blumberg says, including teasing out when prebiotic becomes biotic.

The NAI's initial request for proposals from institutional

groups representing multiple disciplines brought in 50-plus applications, 11 of which were accepted. In addition to the Ames Research Center, the other lead institutions are Arizona State University, Tempe; the Carnegie Institution of Washington (D.C.); Harvard University, Cambridge, Mass.; the Jet Propulsion Laboratory, Pasadena, Calif.; the Johnson Space Center, Houston; the Marine Biology Laboratory, Woods Hole, Mass.; Pennsylvania State University, University Park, Pa.; the Scripps Research Institute, La Jolla, Calif.; the University of California at Los Angeles; and the University of Colorado, Boulder.

Blumberg is currently also senior advisor to the president of the Fox Chase Cancer Center in Philadelphia, where he was formerly vice president for population oncology and associate director for clinical research—and the recipient for 30 years of an NIH grant for a liver cancer prevention program.

For more information about NAI, visit <http://nai.arc.nasa.gov>. ■

REMEMBERING SIDNEY UDENFRIEND (1918–1999)

by Bernhard Witkop
NIH Scholar

On May 25, friends, disciples, and colleagues of Sidney Udenfriend will gather at Drew University in Madison, N.J., for a memorial to a pioneer in the fields of metabolism and molecular biology.

When James Shannon hired both of us more than 50 years ago to work in the new National Heart Institute, he predicted that our common interests would lead to a successful marriage of organic chemistry and biochemistry. Indeed, our mutual "trypto-fun" started when, in 1953, Udenfriend and Herb Weissbach demonstrated that 1-5-hydroxytryptophan is the natural substrate for aromatic amino acid decarboxylase and converts it to serotonin. At that time, serotonin was suspected to be a novel neurotransmitter, controlling sleep, memory, mood, and other physiological functions. This area of budding research would ultimately lead to the organization of ISTRY—the International Study Group for Tryptophan Research—in 1983.

Tryptophan-5-hydroxylase was another of Udenfriend's studied enzymes. He wanted to assay it by a tritiated substrate in the same way he'd followed the conversion of trans-4-³H-1-proline to 4-OH-proline in the post-translational conversion of procollagen to collagen. However, there was a big surprise, in 1966, when the conversion of 5-³H-tryptophan to 5-OH-tryptophan proceeded with almost full retention of tritium, which was not lost but migrated into the neighboring 4-position. In fairness to all the participating investigators, Udenfriend coined the name of "NIH-Shift" for this unprecedented phenomenon.

The biosynthesis and metabolism of another fundamental neurotransmitter, norepinephrine, fascinated both Udenfriend and Julius Axelrod, who received the Nobel Prize in 1970 for related research. In the formation of nor-epinephrine, according to Udenfriend, the rate-limiting step is hydroxylation of tyrosine. The preceding step, hydroxylation of phenylalanine, is involved in the clinical syndrome of phenylpyruvic oligophrenia, or phenylketonuria. Again, when Udenfriend looked for a rapid assay of phenylalanine hydroxylase by offering it the tritiated substrate 4-³H-1-phenylalanine, tyrosine was formed with more than 95 percent retention of tritium.

The introduction of the "Visiting Pro-

gram" in the late fifties was a boon for NIH and brought us such outstanding postdocs as Siro Senoh, from Japan, who made 6-hydroxydopamine available to Udenfriend and the novel metabolite of norepinephrine, the so-called normetanephrine, available to Axelrod.

When in 1968 Udenfriend accepted the position of director of the Roche Institute for Molecular Biology, he parted from his beloved NIH with a heavy heart. Soon thereafter, he showed his gratitude and attachment by acting as one of the three "godfathers" who helped to name Building 1 the James Augustin Shannon Building.

A less well-known contribution of Udenfriend to NIH was his early recognition of the merits of Marshall Nirenberg, years before Nirenberg received the Nobel Prize in 1968 for deciphering the genetic code, and of Nirenberg's wife, Brazilian biochemist Perola Zaltzman, who worked in Udenfriend's lab and would have left had her husband concluded his search for a position outside NIH. If not for Udenfriend's finding places for Nirenberg and Zaltzman at the Heart Institute, NIH would have lost them both. ■



From the Archives: Bernhard Witkop (left, the author) receives the Hillebrand Award on March 12, 1959, from American Chemical Society past president Joseph Spies (center). Sidney Udenfriend (right) also a Hillebrand awardee, delivered that year's Hillebrand lecture, in which he emphasized the growing links between chemistry and psychiatry with the uncovering of the metabolism of the amino acids tryptophan, phenylalanine, tyrosine, dopa, and histidine.

Other Recollections

■ *Information from an obituary written by Sydney Spector, Herbert Weissbach, and John Burns and published in Pharmacologist 42:45 (2000):*

Sidney Udenfriend was born in Brooklyn, N.Y., April 5, 1918. He got a B.S. from City College of New York and a master's degree and Ph.D. in biochemistry from New York University. As a graduate student, he also worked in the malaria program at the Goldwater Memorial Hospital in New York, where he developed methods to measure blood concentrations of antimalarial drugs. After a time at Washington University in St. Louis, he was invited to NIH, where from 1956 to 1968 he was chief of the Laboratory of Clinical Biochemistry at the National Heart Institute. He then became the first director of the Roche Institute of Molecular Biology, where he remained until 1996.

From 1997 to the time of his death (December 29, 1999), he was director of the Charles A. Dana Research Institute for Scientists Emeriti at Drew University in Madison, N.J. He is survived by his wife Shirley, daughter Aliza, son Elliot, and three grandchildren.

■ *From notes from Alan Peterkofsky, NHLBI, and Phil Chen, OIR:*

Sidney Udenfriend strove for diversity in graduate programs "before [it] became popular." One of his African-American graduate students, named Tom Smith, went on to become chairman of the Biochemistry Department at Howard University in Washington, D.C.

Udenfriend was on the organizing committee of the first NIH alumni reunion, April 1975.

■ *From Herb Weissbach, in response to a question from Alan Peterkofsky:*

"To my knowledge the first 'formal graduate program' was between the [Bernard] Brodie lab and the George Washington University School of Medicine [Washington, D.C.]. Sid was instrumental in setting that up, and I believe I was his first Ph.D. student.

"Some of us received degrees from the Biochemistry Department, others (Julie Axelrod, Ron Kuntzman) from the Pharmacology Department. These were the only departments involved, to my knowledge." ■

COMMENTARY

NIH RESEARCH: THE SPIRIT MAKES ALL THE DIFFERENCE

by Joram Piatigorsky
Laboratory of Molecular
and Developmental Biology, NEI

Why are you crying, son?" asked the gray-haired gentleman when he came upon a little boy in the park. The young boy was no more than five years old. He looked pitiful, with large dewdrops dripping from both eyes and his nose sniffing. He was sitting alone on the edge of the wooden bench. The boy looked up at the gentleman.

"Why are you crying?"

The boy said, "My mommy won't let me climb on the goat statue."

"Why not?" asked the gentleman.

"She says that I could fall off and get hurt. She says that kids aren't supposed to climb on it and if I do the other kids will want to do it too."

"What does she want you to do at the park then?" asked the gentleman, becoming interested.

"She wants me to play with the other kids."

"Don't you want to do that? I see a lot of kids your age running around."

"No. I want to climb on top of the goat."

"What would you do there?"

Long pause. The tears were gone now, and the little boy's eyes had a mischievous gleam.

"I'd sit there and look around and pretend I was exploring. I did it once when my mommy wasn't watching. Everything looked different up there. I could see across the street, and the birds seemed closer. It was exciting. I dreamed that..."

"Yes, go on. What did you dream of?"

The boy's head drooped and then he whispered, "I'm not supposed to talk to strangers—that's my mommy coming."

The gentleman stepped aside and watched as the little boy slid off the bench and walked sullenly away beside his mother. They passed directly in front of the goat, but the boy's stare never budged from the pavement as they disappeared into the distance.

Unfortunately, I believe that many basic researchers resonate with this story. When I came to the NIH almost 33 years ago, such a story about denying dreams and withholding playful exploration would have been foreign to me and to my peers. It was understood

that tinkering with the unknown was the boiling pot of discovery.

Remarkable advances resulting in recombinant DNA technology have made it possible to define nearly every gene and protein in the body, and it takes little imagination to visualize the ultimate conquest of intractable diseases. I presume that there would be wide agreement that we are in the most productive phase of understanding biology that has ever existed. I hardly need to elaborate on this to the NIH audience. So then, I ask myself, "why do I feel sullen in this time of plenty?"

Looking around at my contemporaries, I realize that I am not alone. And when I observe the postdoctoral fellows, the foundation of our future, I don't see many gleams in their eyes. Granted,

work environments differ in small but important ways among the laboratories, but something is not quite right; the mood is not as it should be. Here is a typical scenario.

An eager postdoctoral fellow gets excited about a project involving gene expression during eukaryotic cellular differentiation. Her work progresses, a transcription factor is isolated, but unexpected complexity is revealed. She wants to pursue the general problem in a different organism that may give additional insight. The new experimental system is out of the mainstream, which slows down the generation of data.

Her IRTA time runs low, and the job search begins. She pursues academia, her true love, but is told that if she had a grant in hand, she would be more competitive—perhaps she could adapt her original ideas to address a disease listed as a national priority. She lets go of the fundamental problems she'd been pondering, writes an appropriate proposal, and obtains a job offer. Her proposal is funded.

She carries out a research program, but lacks the enthusiasm that drove her early scientific years. Although she will make contributions to science, she will no longer let her mind roam creatively in mysterious territory. She is not ex-

cited about her work; she is anxious to have her grant renewed.

I recognize the realities of finite resources and the desire for immediate solutions, but

research in science is more than a business. There is a difference between solving a problem and discovering a new phenomenon. The former can be envisioned and exists within our conceptual framework; the latter changes our understanding of the natural world. The progress of science depends on revealing hidden phenomena.

How can we look across the street—or climb the statue and look farther—if we must always play on the pavement with everyone else, doing the same thing?

Certainly science builds on incremental additions to a growing structure of knowledge, and the present novel approaches in genetics are powerful and nothing short of extraordinary. But in my years in the intramural program, I have watched the deluge of technical advances, commercialization, and goal-oriented motives change our research landscape. The banter of daily conversation seems less driven by curiosity than it was back when messenger RNA was being discovered or the genetic code was being revealed. That era, too, as today's, was pregnant with promises for a golden future.

Historically, the NIH intramural program has delivered innumerable scientific advances and has been a source of leadership in research throughout the world. It has done this by permitting investigators to percolate in a well-supported, academically free research environment. Now we are witnessing many creative scientists reaching out to the lucrative offers of commercially driven research. There are also pressures to make rapid links between the bench and the clinic. But one's best work seldom springs from an assignment to meet a deadline on someone else's agenda.

Science may benefit more than ever today by nurturing the adventuresome spirit and curiosity that have been the hallmarks of the NIH intramural program. If not here, then where? ■



Fran Pollner

Joram Piatigorsky



POSTBACCALAUREATE POSTERS: REFLECTIONS OF RESEARCH FUTURES

text and photos
by Cynthia Delgado

April 1994 marked the beginning of the NIH Postbaccalaureate Program. March 2000 marked the beginning of what will be an annual postbac poster session.

Among the youngest of the pre-IRTAs on campus, postbacs are recent college graduates who are considering research careers and whose year or two in an NIH lab is meant to fan the flames of their interest in biomedical research. Ideally, postbacs apply to graduate or medical schools while working in the NIH program.

Sponsored by the Office of Education, the postbac poster session was held in the Clinical Center in conjunction with a Wednesday Afternoon Lecture and showcased the research of about 75 trainees. What follows is a random sample of the presenters and their work. Common themes, on a personal level, were unbridled praise for mentors and the NIH research experience and their pursuit of careers in clinical medicine and research—with a smattering of laments over having to study for the MCAT.

Sherimay Ablan

"Are rafts involved in HIV-1 entry?"



Sherimay Ablan is applying to medical school and describes her lab as "diverse and intellectually stimulating."

Sherimay Ablan's research findings suggest that glycosphingolipids may be involved in the assembly and function of the HIV-1 fusion machine. HIV-1 gains entry into cells via interactions between its envelope glycoproteins, gp120 and gp41, and the CD4 receptor (and other co-receptors) on the host cell membrane. Subsequently, viral glycoprotein oligomers assemble to form molecular scaffolds that serve to precipitate the fusion event between viral and host membranes. The researchers found that by inhibiting the synthesis of glycosphingolipids in the host cells, they could affect

the HIV-1 fusion event and infection. This function could be recovered, however, by the subsequent addition of purified glycosphingolipids to the impaired cells. Additionally, glycosphingolipid-cholesterol-rich domains form phase-separated membrane "rafts" that are suspect sites for viral entry. When human osteosarcoma cells were depleted of cholesterol, they were significantly less susceptible to glycoprotein-mediated fusion.

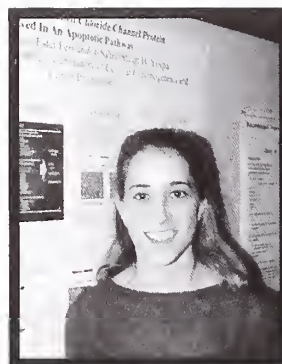
Ablan graduated in the spring of 1999 from the University of Hawaii at Manoa and confided that this was her "first time living away from home." She was encouraged to apply to the pre-IRTA program by a good friend (an alumnus of the pre-IRTA fellowship), as well as by Deborah Cohen, the coordinator of NIH postdoctoral training programs, whom she met while presenting a poster at a National Minority Research Symposium in New York City. She was offered a position in the NCI-FCRDC Laboratory of Experimental and Computational Biology, Membrane Structure and Function Section, under the direction of Robert Blumenthal. Both Blumenthal and staff scientist Anu Puri, she says, "have been great mentors."

Asked about her overall experiences here, she replies with enthusiasm: "It's been great! I work in a very diverse and intellectually stimulating laboratory." She plans to apply to medical school and hopes to "stay on the mainland."

Wendy Bowers

"mtCLIC, a novel p53-regulated chloride channel protein, is involved in an apoptotic pathway"

Wendy Bowers' lab (NCI's Laboratory of Cellular Carcinogenesis and Tumor Promotion) has identified a novel p53-regulated chloride channel protein, mtCLIC, and shown it is involved in apoptosis. When she and her colleagues exposed wild type, neoplastic, or p53 (-/-) null mouse keratinocytes to an apoptotic inducer, VP-16, they saw up-regulation of mtCLIC. Data from these studies suggest that mtCLIC is an "early inducer of apoptosis" and is involved



Wendy Bowers says working at NIH has taught her "a lot of things, most importantly the virtue of patience."

in both a p53-dependent and a non-p53-dependent pathway. Research is currently directed toward the use of an mtCLIC antisense construct to block expression in keratinocytes and other mammalian cells.

Having graduated with a B.A. in sociology (May 1999) from the University of Wisconsin, Madison, Bowers admits that before her NIH experience she knew little about scientific research. A friend who'd enjoyed an NIMH rotation inspired her to "research which doctors were work-

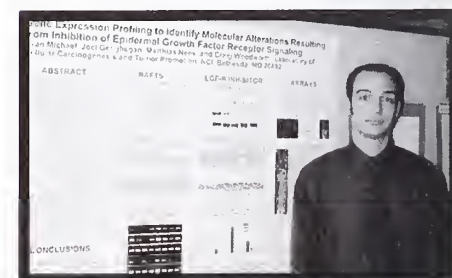
ing in labs that seemed interesting" and to write them. She had several interviews and then chose to work in the LCCTP, with a "great chief"—Stuart Yuspa. She extends particular thanks to her mentor, postdoc Ester Fernandez, remarking that the poster "represents the freedom [Fernandez] has given me in my research and the vast information she has taught me."

Overall, Bowers says, working at NIH has "taught me a lot of things, most importantly the virtue of patience, a quality I hope to maintain as I study to become a clinician." She is applying to medical school.

Evan Michael

"Gene expression profiling to identify molecular alterations resulting from inhibition of epidermal growth factor signaling"

Working in the NCI Laboratory of Cellular Carcinogenesis and Tumor Promotion, Michael studied the effect on tumorigenicity of inhibition of epidermal growth factor receptor (EGFR) signaling. Earlier studies had revealed that "tar-



Evan Michael came to NIH to "experience a real lab first-hand" and was not disappointed.

geted disruption of the EGFR reduces or eliminates tumorigenicity in mouse xenograft models." Using an organotypic collagen raft system, which maintains cell-cell and cell-matrix interactions, as well as state-of-the-art cDNA microarray technology, the researchers examined how signal inhibition of the EGFR alters the morphological and molecular profile of cervical carcinoma. The team has reproducibly identified more than 90 genes that are "up- or down-regulated more than twofold by EGFR inhibition."

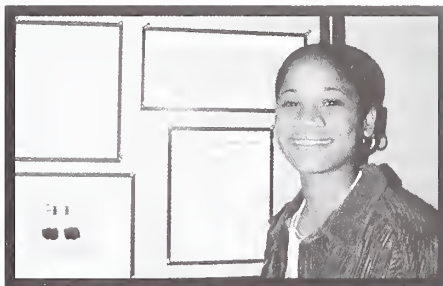
Michael came to NIH from Grinnell College in Grinnell, Iowa, where he graduated with a B.A. in Biology in 1999. He first heard of the postbac program through a letter sent to the graduating seniors by his future mentor Craig Woodworth, about whom he "can't say enough." "He's provided invaluable assistance regarding experimental design and procedures, external resources, and interpreting the results of my experiments—and he gives you the autonomy to make your own mistakes." He also credits postdoc Matthias Nees for having taught him microarray technology.

A major reason for coming to NIH, Michael says, was "to experience a real lab first-hand." As a result of this experience, he has "discovered that I truly enjoy both the benchwork and the intellectual challenges of research." He said he hopes to stay at NIH for a second year and then to enter an MD/PhD program in the academic year 2001.

Tenesha Smith

"Screening for Cx26 mutations in consanguineous Pakistani and Indian hearing-impaired populations"

Tenesha Smith single-handedly screened 301 consanguineous Pakistani and Indian families for Connexin 26 (Cx26) gene mutations known to cause autosomal recessive nonsyndromic deafness, *DFNB1*. The *DFNB1* locus maps to chromosomal interval 13q11-12 and is reported to be responsible for 20–50 percent of cases of autosomal recessive deafness in U.S. and European populations. Although one particular mutation, 35delG, accounts for approximately 70 percent of Cx26 mutant alleles, Smith and her colleagues discovered it was absent from Pakistani and Indian families. Rather, they found that mutant alleles, designated W24X and W77X, accounted for most of these mutations. And, Smith happily announced, she also "found



Tenesha Smith rates her NIH experience "a 10, without hesitation" and advises her peers to "stay focused . . . and never lose faith" in themselves.

three novel mutant alleles that were not previously published."

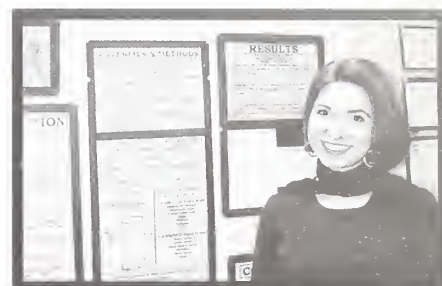
Smith graduated from Clark Atlanta University in 1997 with a B.S. in biology. Her advisor told her about the Partnership Program offered by NIDCD. For the past year, she has worked with mentors Edward Wilcox (staff scientist), Robert Morell (senior staff fellow), and Thomas Friedman (chief) at the NIDCD Laboratory of Molecular Genetics.

She calls her experience at NIH "invaluable" and rates it "a 10." She says it has "reinforced" her decision to go into an MD/PhD program. Clinically, she is drawn to both primary care practice and orthopedic surgery.

Kim Wittenberg

"The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid of rhesus macaques (*Macaca mulatta*): How strongly does it predict alcohol tolerance?"

One of Kim Wittenberg's major projects at the NIAAA Laboratory of Clinical Studies, Primate Section, examined the relationship of cerebrospinal fluid (CSF) 5-HIAA concentrations and alcohol tolerance. Each of 88 rhesus macaques underwent two identical trials in which they were given an intravenous ethanol solution and then rated for tolerance determined by behavioral measures, such as escape challenge, locomotive, and aggressive behaviors. Their data revealed that CSF 5-HIAA concentrations were positively correlated with a change in alcohol tolerance between trials 1 (inherent tolerance) and 2 (acquired tolerance). Thus, animals with low concentrations of CSF 5-HIAA had little change in alcohol tolerance between the two trials, whereas animals with high concentrations had a greater



Kim Wittenberg's focus has "shifted" toward medical research, and she'd like to move from dolphins and macaques to other humans.

change in alcohol tolerance between trials. The data also corroborated earlier studies that demonstrated that CSF 5-HIAA concentrations are negatively correlated with future alcohol consumption and inherent alcohol tolerance. Wittenberg notes that "further studies are needed to fully understand what mechanisms influence alcohol tolerance."

Wittenberg received a B.A. in biology from Lawrence University in Appleton, Wisc., in 1994 and an M.A. in Biology from Boston University in 1997. After working with dolphins in Hawaii, she came to NIAAA in Poolesville, where she has been working with rhesus macaques. She thanks her mentor, research psychologist James Higley, for providing not only training but "sincere encouragement." She learned of the program at the Science Online web site.

Her experience at NIH, she says, has "shifted [her] focus toward medical research." She's considering seeking a PhD in neuropsychology and hopes to work with humans in a clinical setting. ■

Metals in Medicine

NIGMS and several other NIH components are hosting a meeting on "Metals in Medicine: Targets, Diagnostics, and Therapeutics," June 28–29, 2000, at the Natcher Conference Center, to explore the role of metals in the development of therapeutic drugs and in vivo diagnostic agents. For a printable meeting flyer and list of speakers, topics, and registrants, visit <http://pub.nigms.nih.gov/MIM>, where online registration is available and encouraged. For more details, contact organizer Peter Preusch at (301) 594-5938 or preuschp@nigms.nih.gov. ■

this purpose, the scientific directors are expected to track the participation of their staff in the organization of electronic publications and submission of non-peer-reviewed material for electronic distribution.

V. Establishing an Electronic Journal

The current PubMed Central system permits any group consisting of at least three senior scientists (independently funded investigators) to establish an electronic journal which will be automatically included in PubMed Central. This raises the question of whether IRP scientists should be permitted to use this new opportunity and, if so, whether any special requirements need be met before doing so.

With respect to publication activities, in general, IRP scientists enjoy the same academic freedoms as their extramural colleagues. Specifically, IRP scientists may serve as editors or members of editorial boards of existing journals, after the appropriate approval either as an outside activity or as part of their official duties. Involvement in electronic journals, including new ones, should be handled no differently, and IRP scientists should be permitted to establish electronic journals.

To ensure that such activities do not compromise the NIH or PubMed Central or the association between the two, the following are recommended:

- An IRP group wishing to establish a new journal should include at least three tenure-track or tenured scientists.

- Proposals for new journals, which are likely to include a policy statement, instructions for authors, and, perhaps, an inaugural editorial article, should be reviewed and cleared within the appropriate ICs in the same way as is currently done for manuscripts submitted for publication.

- Establishing a new e-journal qualifies as an outside or official activity and should require approval by the same mechanisms that already exist for other professional activities.

- To avoid the appearance of a conflict of interest stemming from the connection between NIH and PubMed Central, new e-journals edited by IRP scientists should include a prominent disclaimer stating that the views and opinions expressed in the journal do not necessarily conform to those of NIH or the U.S. government.

- For the same reasons, the inclusion of non-NIH scientists among those administering the journal, and sensitivity to the appearance of conflicts of interest in the selection of referees for IRP-authored manuscripts, is strongly advised.

V. Participation in an E-Journal

As an Author: Clearance and Submission of Manuscripts. The choice of where to publish NIH research has traditionally been the prerogative of the authors, in consultation with colleagues and supervisors. The advent of electronic publishing is no reason to change this policy or in any way restrict the choices of NIH scientists in their selection of the best forum for airing their findings. In general, research reports should be published in peer-reviewed journals.

Because there should be no difference in the quality or rigor of electronically compared to conventionally published research, authors should follow the same procedures for NIH review and clearance of electronic publications as are followed for traditional publications. Clearance procedures

were recently reviewed by a subcommittee of the scientific directors and simplified to a check sheet that can be amended or used as is by the institutes. The manuscript clearance can be found at this web address:

<http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/outside-act.htm>.

Some institutes have amended the check sheet procedures, but all should have in place a system for timely review of publications prior to submission. Where the in-house review process is backlogged, lengthy, or burdensome, institutes should streamline and delegate the review workload more efficiently. The potentially shorter time-course and increased volume of electronic publications—and the potential increase in submissions of material that will not be subject to further peer review (see Section V)—intensify the need for prompt, careful clearance.

As an Editor or Reviewer. Editing or reviewing articles for an electronic journal raises no special issues relative to editing a conventional journal and may be carried out either as part of one's official duties or as an outside activity. A good guide to what is and is not allowed for official duty activities and outside activities may be found at

<http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/outside-act.htm>.

Given the ease of mass distribution of documents via e-mail, reviewers and editors should be extremely careful when they address and electronically send manuscripts and reviews to avoid accidental release of pre-publication data.

VI. Posting of Non-Peer-Reviewed Material

Background. Currently, PubMed Central is not accepting non-peer-reviewed material. However, the committee is aware of at least three journals (one conventionally published, two electronic) that are now accepting non-peer-reviewed material, or will soon. Though there are concerns about publishing non-peer reviewed results in the new online formats, it should be noted that IRP scientists, like their extramural colleagues, already regularly publish or otherwise publicize non-peer-reviewed material in reviews, some abstracts, and articles in conference proceedings, and deposit non-reviewed data such as nucleotide sequences or x-ray coordinates in various data banks. Attempts to limit these contributions especially to repositories would be detrimental to science. It is unclear whether, in the field of biomedical research, the publicizing of non-reviewed material in online journals will mushroom or if it will have harmful effects. The committee recommends that the individual institutes track such contributions by their own staff and that the OIR review the matter one to two years from now.

Non-Clinical Data. NIH authors should weigh carefully the ramifications of publishing their results in non-reviewed electronic publications. For very theoretical reports submitted to a discerning online audience of peers and colleagues, errors may be quickly spotted, discussed, and corrected. For very specialized research with limited response, it may take much longer for errors to be uncovered in a non-peer-reviewed e-journal. For research of high interest to the lay public, unreviewed findings may be disseminated widely before errors are caught and may be misinterpreted and taken out of context.

In any case, there should be no lowering of the standards of quality for NIH research that goes into journals, whether these are rigorously reviewed or minimally screened. It is particularly important that the Institute's internal procedures for clearance of manuscripts be strictly adhered to for material that will not

be otherwise reviewed.

Clinical Research. Manuscripts submitted by author(s) from the NIH that will receive no further peer review before posting and that report results of research studies involving the use of human subjects or materials should receive special attention because the potential cost of error in the scientific record is very high. They should be rigorously peer reviewed by individuals with expertise in the area of the study, either from another branch or laboratory within the same IC or from other ICs or the extramural community.

All manuscripts involving clinical research should include a statement that the study was approved by an Institutional Review Board (IRB) and should provide the approved NIH protocol number. Manuscripts should seek to protect patient confidentiality in any text, figures, or images. In addition, for all clinical studies, investigators should include a statement that all applicable regulations and institutional rules regarding protection of human subjects have been followed.

If the study was conducted with the support of nonfederal funds, then this information should be stated in an appropriate place consistent with the journal or PubMed Central guidelines. All manuscripts should identify the

author(s), their section, branch, laboratory, institute or center, academic affiliation (for non-NIH collaborators), and contact information.

It is recommended that all clinical research studies contain the following information:

- background, including whether the trial is phase I, II, or III
- objective or statement of the problem
- information about subject recruitment, selection, and, when applicable, randomization
- statistical test(s) used
- results (both positive and negative)
- conclusions
- references

VII. Other Comments

Although outside professional activities are currently subject to approval, it is uncertain whether publications stemming from such activities are regularly subjected to the institutes' procedures for clearance (see "Current Procedures for Overview of Publishing Activities by NIH Staff"). The Committee recommends that all such material either be submitted for clearance or include a prominent disclaimer stating that the views and opinions expressed do not necessarily conform to those of NIH or the U.S. government. ■

Current Procedures for Overview Of Publishing Activities by NIH Staff

Submission of manuscripts as part of official duties

Under "administrative procedures" (F3) of the Annual Survey of Managerial Controls, each institute's intramural research program is asked, "Do you have a procedure for clearance of manuscripts submitted for publication to provide assurance that all federal policies and regulations are followed as specified by the Board of Scientific Directors?"

In October 1997 the Board of Scientific Directors decided that rather than trying to revise the outdated Manual Issuance they would develop a standard approval form that would contain the minimal information to be included in the request for approval (see <http://www1.od.nih.gov/oir/sourcebook/oversight/pub-clear.htm>).

This was incorporated into a standard form (approved by the SDs at their meeting of March 4, 1998) that is available through the NIH web site:

<http://www1.od.nih.gov/oir/sourcebook/oversight/pub-clear-form.htm>.

Submission of manuscripts other than as part of official duties

Employees are expected to get approval for specific "outside" professional activities, but it is not clear that if such an activity includes submission of written materials for public distribution, approval for such writings is regularly sought.

Performance of editorial activities as part of official duties

Such activities are approvable, assuming that the job description includes editorial activities as appropriate. It is not clear that anyone monitors to see whether the publication with which the individual plans to be associated is a "worthy" one, or even known.

Performance of editorial activities as an "outside" activity

Employees are expected to get approval for specific "outside" professional activities. It is not clear that anyone monitors to see whether the publication with which the individual plans to be associated is a "worthy" one, or even known. ■

Missing from the Stacks

The NIH Library maintains a collection of annual reports from all the intramural programs—but doesn't have a complete set. Especially in earlier decades, there are gaps in what would otherwise be a comprehensive history of NIH intramural research.

Following is a list of all the annual reports that were never received by the Library, with a plea from NIH historian Victoria Harden, harden@od.nih.gov, and NIH Library Branch Chief Suzanne Grefsheim, sg8d@nih.gov, that holders of these volumes consider donating them to the NIH Library in Building 10.

NIAID

1963 1964 1965 1966 1969 1970

NIAAA

All reports after 1994 missing

NIAMD (Now NIAMS)

1961 1962 1963 1964 1965 1966
1969 1970 1981

NCI (reports appear to have been issued in two volumes each year)

1957 1961 1962 1963 1964 1965
1966 1969 1970

NICHD

1967 1969 1970 1983 1991

NIDR (Now NIDCR)

1958 1961 1962 1963 1964 1965
1966 1967 1970 1971 1976 1990
1991

NIDA

All reports after 1994 missing

NIGMS

1970 1973 1974 1976 1977 1978
1983 1984 1986 1987

National Heart Institute

1961 1962 1963 1964 1965 1966

National Heart and Lung Institute

1969 1970

NIMH

1961 1962 1963 1964 1965 1966
1969 1970

Reports after 1983 on Internet?

NINDB (Now NINDS)

1961 1962 1963

NINR

Reports after 1996 on Internet?

Clinical Center

1953 1954 1955 1956 1957 1959
1960 1961 1962 1963 1964 1969
1970 1973 1983 1991

Division of Computer Research and Technology

1970 1972 1983

Division of Research Grants

1974

All volumes after 1984 are missing

Division of Research Resources

1973 1974 1975 1977 1978

All volumes after 1984 are missing

Division of Research Services

1960 1961 1962 1963 1964 1967

DRS, Biomedical Engineering and Instrumentation Branch (report filed separately)

1982 1984

NCRR

1991

Division of Biologics Standards

1957 1958 1959 1961 1962 1963
1964 1965 1966 1967 1970

RECENTLY TENURED

Zbigniew Dauter obtained his Ph.D. from the Technical University of Gdansk, Poland, in 1975. He lectured on crystallography at that university, then conducted research on structures of biologically active small and macromolecules at the University of York, England. He also worked at the synchrotron outstation of the European Molecular Biology Laboratory in Hamburg, Germany, before coming to the United States and assuming his current position as chief of the new Synchrotron Radiation Research Section within the Program of Structural Biology of the NCI in Frederick. His group is located at the synchrotron of Brookhaven National Laboratory on Long Island, N.Y.

My interests have always been in the elucidation of the structures of biologically active compounds—at first, smaller organic ones, such as antibiotics and anti-tumor acridine derivatives, and for the past 18 years, macromolecules. I specialize in the application of the unique properties of the synchrotron X-radiation to diffraction studies of macromolecular crystals, in particular, atomic-resolution structural analyses and use of anomalous scattering effects.

The enormous intensity of X-rays produced by the synchrotron makes it possible to record diffraction data on protein crystals at atomic resolution—about 1 Å. This provides a wealth of structural information with the accuracy in the range of 0.01 Å, comparable with the structures of small molecules. This leads to improved libraries of protein stereochemistry and provides better target values of geometrical parameters for validation of protein models refined at lower resolution.

Many hydrogen atoms become directly visible in electron density maps generated with the synchrotron. This is important because hydrogen atoms are very often crucially involved in the reaction mechanism of enzymes. Atomic resolution also allows investigation of the protonation states of charged groups within the protein. I have participated in several studies of macromolecular structures at atomic resolution of proteins ranging from small metalloproteins (rubredoxins and ferredoxins) to larger enzymes. The 1.0-Å model of 75-kDa alcohol dehydrogenase complexes has

led to revision of the classic mechanism of this enzyme.

Another property of synchrotron radiation is its tunability, which makes it possible to capitalize on anomalous dispersion effects of heavier elements inherently present or introduced into proteins. This is the basis of the popular multi-wavelength anomalous dispersion method of solving crystal structures. We recently devised a novel modification of this approach, based on incorporation of anomalously scattering bromide or iodide ions into protein crystals. We incorporate the ions into the protein crystals with a flash dip in the appropriate cryosolution. This approach may be particularly useful for high-throughput projects, such as structural genomics. Several new structures have been recently solved with this approach. For example, the structure of the yeast hypothetical protein yhp9 containing the GAF domain, with a dimer of 2 times 18 kDa in the asymmetric unit, has been



Zbigniew Dauter

solved from NaBr-soaked crystals by Jim Hurley and his team at NIDDK, and the results are being prepared for publication in *Cell*.

Also, the structure of the human acyl-protein thioesterase of 56 kDa (see figure for a piece of the initial electron density map with a fragment of a β -sheet) was recently solved from brominated crystals using single-wavelength data in the laboratory of Zygmunt Derewenda of the University of Virginia in Charlottesville (the protein came from Teresa Jones of NIDDK). It will be published in *Nature Structural Biology*.



The applications we work with demand diffraction data that are as accurate as possible. Optimization of data collection procedures is my particular specialty. By recording very accurate diffraction data on lysozyme crystals and by using very small anomalous signals of sulfur and chlorine atoms, we have shown lysozyme binds several halide anions at the surface.

In addition to pursuing my own research interests, I am the facility manager for the macromolecular crystallography synchrotron beam line X9B at

Brookhaven. I supervise data-collection facilities that are available to all intramural NIH laboratories (at present about 12 groups) that need to use synchrotron radiation for crystallographic data collection. To obtain more information about access to this beam line, contact me at <dauter@bnl.gov> or (631)-344-7367. I would be glad to collaborate with those interested in crystal structures of their macromolecules.

Chuxia Deng received his Ph.D. from the University of Utah in Salt Lake City in 1992 and did postdoctoral work in Philip Leder's laboratory at Harvard Medical School in Boston before joining the NIDDK Laboratory of Biochemistry and Metabolism in 1995. He is now a senior investigator in the Mammalian Genetics Section, Genetics of Development and Disease Branch, NIDDK.

I am interested in studying human skeletal dysplasias and breast cancer using mouse models. A particularly exciting focus of current research in my laboratory are mechanisms of *BRCA1*-associated tumorigenesis. About half of familial breast cancer cases and 90 percent of combined familial breast and ovarian cancers are associated with mutations in the *BRCA1* gene.

The lack of a suitable animal model has made it difficult to identify how *BRCA1* mutations affect the timing and process of tumor development. Speculations that *BRCA1* is not a simple tumor suppressor and that *BRCA1*-associated tumor formation is not straightforward are fueled by the fact that mice heterozygous for *BRCA1*-null mutations do not develop tumors, while mice homozygous for mutations die early in embryonic life and display cellular proliferation defects.

To plumb the molecular mechanisms through which *BRCA1* represses tumor formation, we introduced a series of mutations—including a null mutation, an isoform mutation, and a conditional mutation—into the mouse *BRCA1* locus. Mutational analyses at both cellular and whole animal levels demonstrated that the primary function of *BRCA1* is to maintain genome integrity through its control over the G₂-M cell cycle checkpoint and centrosome duplication. *BRCA1* mutations result in genetic instability (DNA damage and chromosomal aneuploidy), which then activates cellular protection mechanisms, including cell-cycle checkpoints

and programmed cell death, to eliminate the mutant cells. This is why *BRCA1* mutant cells fail to grow in culture. On the other hand, the genetic instability in *BRCA1* mutant cells theoretically increases mutation rates of all genes, including tumor suppressors and oncogenes, and this increase ultimately overcomes the proliferation defects caused by the *BRCA1* loss and results in tumor formation. Studies in our animal model, whose *BRCA1* is specifically mutated in mammary epithelium, indicate that this is the case.

Analyzing mammary tumors from the *BRCA1*-conditional knockout mice, we noticed that two-thirds of the tumors exhibited alterations in p53, a potent tumor suppressor that is mutated in more than 50 percent of all human cancers. This observation suggests that p53 tumor suppressor gene is involved in *BRCA1*-associated tumorigenesis. To directly test whether inactivation of p53 contributes to the *BRCA1*-associated tumorigenesis, we deleted one wild-type allele of p53 in the mice with mammary epithelium-specific inactivation of *BRCA1*. We found that the remaining wild-type allele of p53 was quickly mutated, and the mammary tumor formation was dramatically accelerated. These results demonstrate that disruption of *BRCA1* allows p53 (and other unidentified genes) to mutate more readily and leads to tumor formation. We plan to use the *BRCA1*-conditional mutant mice to further study molecular aberrations arising from *BRCA1* deficiency, to identify genetic modifiers and exogenous factors that influence the onset of tumor formation, and to validate potential therapeutic strategies.

We have also generated mouse models mimicking achondroplasia, Pfeiffer syndrome, and thanatophoric dysplasia I and II. Our research is elucidating the role of fibroblast growth factor receptors (FGFRs) and TGF β /Smads signals in mammalian development and skeletal formation and is furthering our understanding of the mechanisms underlying dwarfism. FGFRs are membrane-spanning tyrosine kinases that serve as high-affinity receptors for at least 22 growth factors. It has been shown that missense mutations in three out of four known FGF receptors (FGFR1-3) are responsible for at least nine human inher-



Chuxia Deng

ited skeletal dysplasias, including the FGFR3-associated achondroplasia, which is the most common form of dwarfism. Using our mouse model, we demonstrated that a loss-of-function mutation of FGFR3 resulted in faster and prolonged growth of long bones of the arms and legs—phenotypes that are opposite to those displayed in human achondroplasia patients—suggesting that the human diseases are caused by gain of function, or a constitutive activation of FGFR. This hypothesis has been supported by other investigators, as well as by further studies in our own lab. Our work has also demonstrated that the activated FGFRs retard long-bone growth by activating Stats (signal transducer and activator of transcription) and cell cycle inhibitors. We are currently searching for potent inhibitors of FGF/FGFR signals and downstream modifiers in order to develop effective therapeutic approaches for these skeletal dysplasias.

Mustafa Dosemeci received his Ph.D. in occupational health from the Hacettepe University, Turkey, in 1982 and did postdoctoral work on exposure assessment at the London School of Hygiene and Tropical Medicine in the United Kingdom before joining the NCI Environmental Epidemiology Branch in 1986. He is now a senior investigator in the Occupational Epidemiology Branch, NCI.

My research career has focused on assessing exposure to occupational risk factors in cancer epidemiology. My research activities at NCI fall into four areas: 1) exposure assessment in occupational cancer epidemiology and exposure-related methodological issues; 2) large interdis-

disciplinary case-control studies that examine the interaction of genetic susceptibility and occupational and environmental exposures in cancer risk; 3) evaluation of cancer risks in large surveillance studies; and 4) other scientific activities, including chairing the Exposure Assessment Working Group of the Division of Cancer Epidemiology and Genetics.

I have assessed various occupational and environmental exposures for numerous case-control, cohort, and cross-sectional biomarker studies conducted ei-

ther in the branch or in other research institutes around the world. Cohort and case-control approaches have their own advantages and disadvantages. Assessing exposure retrospectively in cohort studies is time consuming and requires careful evaluation of substantial historical exposure information. Because of the availability of monitoring data, exposure assessment in cohort studies typically is considered superior to estimates in case-control studies where we usually lack monitoring data.

In most cohort studies, however, assessment of exposure is specific only to the job title level, in contrast to case-control studies, in which the availability of subject-specific exposure information allows evaluation of between-worker variability within the same job category. Between-worker variability reflects both genetic variability and differences in external exposures to environmental and occupational cancer risk factors; my recent research activities have focused on the estimation of the internal dose of occupational and environmental risk factors in cancer epidemiology.

I have completed quantitative assessments of historical exposure to benzene for 75,000 workers and to silica for 68,000 workers in cohort studies conducted in China and am currently conducting quantitative exposure assessments for three major cohort studies: the Agricultural Health Study, the Diesel Exhaust Cohort Study, and the

Shanghai Women's Cohort Study.

I have also conducted subject-specific assessments of exposure to various solvents, particulates, and industrial chemicals in seven case-control studies and have developed job exposure matrices (JEMs) for more than 40 chemical and physical haz-

ards. In three cross-sectional biomarker studies conducted in China and India, we have assessed exposures to benzene, butadiene, and benzidine and their relationship to biological markers. I have also carried out studies to validate the exposure assessment methodologies we've used in our cohort and surveillance studies. Moreover, based on the results of studies simulating exposure misclassification, we have been able to develop specific recommendations for industrial hygienists to reduce the ef-



Mustafa Dosemeci

fects of misclassification on risk estimates.

Two large interdisciplinary case-control studies are under way to evaluate bladder and lung cancer risks using external and internal doses of occupational and environmental exposures. The first, based in Spain, is a study of bladder cancer that will involve 1,500 cases and 1,500 controls from 18 hospitals. Using a state-of-the-art, computer-assisted technique, information will be obtained by personal interview on occupational, environmental, clinical, and dietary risk factors; blood samples will be collected to determine genetic susceptibility markers.

The second study examines lung cancer risk factors in Russia and is autopsy based. In the pilot phase of the study, we are identifying 500 lung cancer cases and 500 control subjects from 88 hospitals with a high autopsy rate. For this study, I have been collecting work and residential histories and measurement data on more than 100 occupational and environmental hazards and am also obtaining normal and tumor tissue samples to identify genetic susceptibility markers.

I also coordinate three large mortality and cancer linkage databases: One uses death certificate data from 24 states and includes occupational information for about 7.2 million individuals who died between 1984 and 1996; another, a Swedish cancer and environmental linkage database, contains occupational information from the 1960 and 1970 censuses; and the third, the Shanghai Cancer Registry, uses JEMs geared to working conditions in China to evaluate the risk of specific cancers in relation to occupational categories or exposures. These activities afford opportunities to collaborate with intramural and extramural investigators in various hypothesis-generating studies.

Maribeth Eiden received her Ph.D. in genetics from the George Washington University in Washington, D.C., in 1985. She is now chief of the Unit on Molecular Virology in the Laboratory of Molecular and Cellular Regulation, NIMH.

I am interested in the molecular mechanisms of retroviral entry into mammalian cells. Viral entry is a multistage process that involves a series of interactions between viral envelope proteins and cell surface receptors, and later viral core proteins and intracellular pro-

teins, resulting in delivery of the nucleocapsid to intracellular compartments appropriate to activation of reverse transcriptase and synthesis of proviral DNA.

My studies on molecular determinants of retroviral entry began during my doctoral work with Marv Reitz in the Laboratory of Tumor Cell Biology, NCI. My research there characterized the gibbon ape leukemia virus (GALV), the first known retrovirus to be associated with a primate leukemia.

The simplicity of the GALV particle—a virion made up of only three components (genome, core, and envelope)—makes it amenable to use in the construction of hybrid retroviral vectors. A hybrid vector contains genome, core, and envelope components derived from different viruses.

My NIMH lab has focused on the use of GALV vectors to probe cellular requirements for viral entry. To accomplish this, we constructed a series of GALV retroviral vectors. These vectors, like wild-type GALV, are capable of infecting appropriate target cells. Unlike their wild-type counterparts, however, they fail to replicate after infection. The first GALV vectors were produced using PG13 packaging cells. PG13 cells are murine NIH3T3 cells that have been engineered to stably express GALV envelope in combination with murine leukemia virus (MLV) core proteins. The hybrid vectors produced from PG13 cells contain MLV core and genome components in combination with GALV envelope proteins. These hybrid vectors were demonstrated to be capable of infecting several target cells that were resistant to or inefficiently infected by retroviral vectors bearing MLV envelope proteins. We later cloned a full-length, biologically active GALV genome from which we were able to construct a GALV-based packageable genome. Vectors produced in human 293T cells containing this modified GALV genome in combination with GALV core and envelope components are more efficient gene-transfer vehicles than either MLV-based vectors or PG13-produced GALV hybrid vectors for a variety of animal cell types, including human.

Working with Wayne Anderson's laboratory in NCI, we determined that the



Fran Pollner

Maribeth Eiden

GALV receptor normally functions as a type III phosphate transporter. Type III Pi transporters are present on most cell types, where they absorb Pi from interstitial fluid during normal cellular processes such as cellular metabolism, signal transduction, and nucleic acid and lipid synthesis. We and others later discovered that type

III Pi transporters serve as receptors, not only for GALV but also for feline leukemia virus type B, two murine leukemia viruses, and simian sarcoma-associated virus. This finding allowed us to investigate specific features of viral entry shared by GALV and other retroviruses that also use this receptor-transporter family for entry into mammalian cells.

At this writing, it appears that GALV entry requires not only primary binding of the GALV envelope, but also secondary receptor interactions that allow the initial virus-receptor interaction to progress through a series of additional steps that culminate in the release of the nucleocapsid into the cytosol of the infected cell.

My lab has steadily increased its facility in the use of retroviral vectors to infect cells as we have constructed and tested new hybrid vectors. I expect this will lead us to the discovery of additional stages in the multistep process of viral entry. I also expect that we will identify new intracellular protein actors in the process, as well as develop increasingly efficient viral vectors.

Susan Pierce received her Ph.D. from the University of Pennsylvania in Philadelphia in 1977 and was the William and Gayle Cook Professor of the Biological Sciences in the Department of Biochemistry, Molecular Biology and Cell Biology at Northwestern University in Evanston, Ill., before joining NIAID as chief of the Laboratory of Immunogenetics in December 1999.

The long-standing interest of my laboratory is in the molecular mechanisms by which B lymphocytes are stimulated by the encounter with a foreign antigen to proliferate and differentiate into antibody-secreting plasma cells and memory B cells.

It is well established that activation of B cells requires the binding of foreign antigen to the B-cell antigen receptor

(BCR). We now understand that the BCR plays a dual role in B-cell activation by T-cell-dependent antigens: It initiates signal transduction cascades and it transports antigens to an intracellular compartment in which peptide-MHC class II complexes are assembled. The subsequent expression of the peptide-class II complexes on the B-cell surface allows the B cell to engage antigen-specific helper T cells, a critical event in B-cell activation.

We have focused our efforts over the last several years on delineating the cellular and molecular mechanisms underlying the signaling and antigen-targeting functions of the BCR and the means by which these functions are regulated. We hope that understanding these critical BCR processes and their regulation at a molecular level will lead to new strategies for vaccine design to stimulate antibody responses to both pathogens and tumor cells and for therapeutics to block or modify B-cell responses in allergy, autoimmunity, and transplantation.

Evidence from our lab and others indicates that the signaling and antigen-transport functions of the BCR are not independent and that correct targeting of the BCR to the class II peptide-loading compartment requires signaling. Indeed, BCR signaling dictates the correct targeting of antigen, the rate of transport of the BCR, and the efficiency of the assembly of peptide class II complexes.

In addition, B-cell co-receptors that influence BCR signaling in vivo and in vitro—including the FcγRIIB, CD19/CD20, and CD40—also influence antigen targeting. Thus, the B cell integrates information from a variety of signaling receptors to regulate its BCR signaling and antigen-processing function and, in turn, its interactions with helper T cells.

In addition to the B cell signaling receptors, antigen processing in B cells is regulated by several other factors, including the developmental state of the B cell, induction of the stress response, and



Susan Pierce

viral infection.

The observation that the signaling and targeting functions of the BCR are interrelated raised the question of how these two functions are coordinated. Recent advances in cell biology have led to the description of sphingolipid- and cholesterol-rich membrane micro-

domains, or lipid rafts, within the plasma membrane that act as platforms for receptor signaling and trafficking.

We have recently shown that upon cross-linking, the BCR is translocated into lipid rafts in which the Src family kinase Lyn is concentrated and the phosphatase CD45 is excluded. The BCR is phosphorylated in the raft and subsequently targeted to the peptide-loading compartment.

We believe the translocation of the BCR into lipid rafts, although previously unappreciated, could be a control point in BCR function and thus a very significant step in the BCR signaling and antigen processing pathways. Indeed, our recent results indicate that the lipid rafts function to coordinate the activity of the BCR and other B-cell coreceptors and to modulate BCR function during development and during infection by Epstein-Barr virus.

In the future, we plan to use a combination of biochemical and genetic tools to characterize the components of the lipid rafts, their relationship to the BCR signaling pathway and antigen-targeting pathways, and their function in immature and memory B cells. ■

Hispanic Scientists: Cinco de Junio

The first-ever NIH Hispanic Scientists Day, in recognition of scientific contributions by Hispanics in the NIH Intramural Program, is scheduled for Monday, June 5, 10:30 a.m.–1:00 p.m. in Building 10, Lipsett Amphitheater. The activity will begin with a seminar—"A Framework for Fc Receptor Signaling: A Complex Story"—at 10:30 a.m. by Juan Rivera, senior investigator and head of the Signal Transduction Group, Chemical Immunology Section, Arthritis and Rheumatism Branch, NIAMS. Poster presentations by Hispanic postdoctoral fellows and postbaccalaureate trainees will follow from 11:30 a.m. to 1:00 p.m.

The event is sponsored by the NIH Fellows Committee and the NIH Hispanic Employee Organization. For more information, please contact Nancy Vazquez-Maldonado at (301) 827-1774, or e-mail: <vazquez@cber.fda.gov>.

Catalyst Quarters

Reminder: The NIH Catalyst has two new locations:

On earth, Building 2, Room 2W23
In cyberspace,

<<http://catalyst.cit.nih.gov/catalyst/>>

National Institutes of the P.I. Blues (Notes from the front lines)

DENT

IF YOU'VE NOTICED ANYTHING WRONG WITH THIS FEATURE LATELY, IT'S BECAUSE...



THERE'S NOTHING FUNNY ABOUT BEING A P.I.!!!

THIS IS A SERIOUS BUSINESS—LIVES DEPEND ON WHAT I DO! ON HOW WELL I WRITE MY GRANTS—ON WHETHER I CHOOSE THE RIGHT EXPERIMENTAL APPROACH—ON HOW MUCH TIME I SPEND IN FRONT OF MY COMPUTER—

PRINTING OUT FORMS, MAKING FIGURES AND DIAGRAMS AND SCHEMES—

ANALYZING DATA—AND NO I WOULD NEVER MANIPULATE THE DATA TO MAKE IT LOOK BETTER THAN IT REALLY IS. BECAUSE SCIENCE IS THE TRUTH AND SCIENCE IS MY LIFE, AND... LET'S FACE IT—I'M JUST A PATHETIC WORM TRYING TO SCRATCH OUT A MEAGER



LIVING IN POOR SOIL... WHO WOULD HAVE THOUGHT BEING AN NIH POST-DOC WAS THE GOOD OLD DAYS?

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: the pursuit of business versus the pursuit of answers in scientific research, e-publishing, retirement, and Interest Group updates.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:

**<catalyst@nih.gov>;
fax:402-4303; or mail:
Building 2, Room 2W23.**

In Future Issues...

- July Update:
Interest Groups
- Leave It and Love
It: Retirement
- Ombuds Business

1) In two articles in this issue ("Clone Rangers," page 1, and "The Spirit," page 7), scientists lament a growing emphasis on practical and profitable applications of biomedical research, with concomitant neglect of basic questions. Do you agree with this portrayal? How would you revise it?

2) What critiques would you offer on the e-publishing guidelines? Would you encourage a colleague to publish in a non-peer-reviewed e-journal? Why or why not?

3) *The NIH Catalyst* is planning a special issue on retirement and how retired scientists conduct their lives after they leave the campus. Do you have any anecdotes or plans of your own?

4) This is not so much a question as a request to Interest Group contacts. Each July, the *Catalyst* runs an updated Interest Group Directory. Everyone who was listed as a first contact for any of the 86 Interest Groups included in the July-August 1999 issue will soon receive a copy of last year's listing to verify or change, as needed. If your new group is *not* on the list send the *Catalyst* its name and web address; regular meeting time and place; and the name, phone number, and e-mail of the contact person. Changes and new information must be received by June 24th to be included in the July-August 2000 issue.

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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